REMARKS

Applicants respectfully request consideration of the foregoing amendments and the following commentary, in the context of continued examination of the present application.

I. Status of the Claims

Claims 3, 5, and 7-19 were cancelled previously. In an effort to advance prosecution, claims 20, 22, and 23 have been amended to delete mention of hybridoma FERM BP-8268, without prejudice to or disclaimer of that subject matter. Thus, applicants reserve the right to pursue any cancelled subject matter in one or more continuing application.

Because no new matter is introduced by these changes, applicants respectfully request entry of the present amendment. Upon entry, claims 1, 2, 4, 6, and 20-25 will be pending, with claims 1, 2, 4, and 6 withdrawn from examination.

II. Rejection of Claims under 35 U.S.C. §102(b)

Claims 23-25 remain rejected for alleged anticipation by WO 01/66596 to Itoh *et al.*, as evidenced by Yu *et al., Endocrinology* 146: 4647-56 (2005), and Mohammadi *et al., Cytokine Growth Factor Rev.* 16: 107-37 (2005). Applicants respectfully traverse the rejection.

The antibodies prescribed by claims 23-25 are (i) competitive with the antibody produced by hybridoma FERM BP-7838 or FERM BP-7839 and (ii) capable of neutralizing the FGF-23 activity.

Recitation (i) reflects or embodies salient structural aspects of an antibody as claimed, *i.e.*, those features whereby such antibody competes with the recited, hybridoma-referenced antibodies for the cognate ligand, FGF-23. Grounded in this perspective, the examiner asserts that "the antibodies of Itoh would inherently compete with the instantly claimed antibodies" (final action at page 4, lines 9-10).

Without acquiescing on this point, applicants would emphasize that the examiner has not urged and, indeed, cannot reasonably urge that Itoh's teachings meet recitation (ii) of "neutralizing the FGF-23 activity." Accordingly, the cited art does not establish a *prima facie* case of anticipation.

The examiner asserts that Itoh teaches antibodies that "both bind[] to amino acid residues 1-179 of FGF-23 ***and*** antagoniz[e] FGF-23 activity" (Action at page 4, lines 14 & 15; emphasis added). Looking to pages 30 and 31 of the reference, the examiner purports to find two pieces of supportive evidence: (a) Itoh's antibodies "can be used to treat hypophosphatemic diseases involving overexpression of FGF-23, such as X-linked hypophosphatemic rickets" or XLH (*id.*, lines 6 & 7); and (b) Itoh teaches antibodies "that block FGF-23 activity, for example, in a bioassay" (*id.*, lines 2 & 3).

As to point (a), applicants submit that Itoh actually links XLH, as well as ADHR, not to overexpression of FGF-23 but rather to the expression of FGF-23 variants that are cleaved in an abnormal fashion. *See* reference at page 17, last full paragraph, and page 18, lines 10-27 (*e.g.*, "the inability of mutated FGF-23 to undergo cleavage may contribute to the disrupted phosphate metabolism of rickets and ... other disorders").

Thus, nothing in Itoh implicates a potential therapeutic role for an anti-FGF-23 antibody in this context. Conversely, "overexpression" is mentioned only once, in relation to the

> *...unique ability of antibodies to recognize and specifically bind to target proteins[, which] provides an approach for treating an overrexpression of the protein. Thus, another aspect of the [Itoh] invention provides for a method for preventing or treating diseases involving overexpression of the FGF-23 protein by treatment of a patient with* ***specific antibodies*** *to the FGF-23 protein*

Page 31, second full paragraph (emphasis added). Which "specific antibodies" might work for what diseases goes unexplained.

In fact, Itoh gives no guidance whatsoever about antibodies "that block FGF-23 activity" in a manner that might have therapeutic significance. As to the examiner's point (b), in particular, Itoh does not teach an antibody that "antagoniz[es] FGF-23 activity" *in vivo*. Instead, the reference states that:

> *Polyclonal antibodies can be prepared by immunizing rabbits or other animals by injecting antigen followed by subsequent boosts at appropriate intervals. The animals are bled and* ***sera assayed*** *against purified FGF-23*

> *protein usually by ELISA or* ***by bioassay based upon the ability to block the action of FGF-23 on liver or other cells****....*

Id., first full paragraph (emphasis added).

It is apparent, therefore, that Itoh spoke prophetically about using an undefined "bioassay," relating some *in vitro* "action of FGF-23" that the reference links to no *in vivo* state, in order to obtain ***polyclonal*** antibody, *i.e.*, a combination of different antibodies, from sera. Even if the skilled artisan somehow could have inferred a therapeutic potential for such polyclonal antibody, which seems doubtful, there would have been no reasonable basis for expecting that a ***given*** anti-FGF-23 antibody could "neutraliz[e] ... FGF-23 activity," as claim 23 recites.

Itoh's mention of an undefined bioassay presages no *in vivo* effect for any antibody that Itoh envisages in general. In sharp contrast, the present application describes the significant *in vivo* effects achieved by antibodies produced by hybridomas FERM BP-7838 and FERM BP-7839, respectively.

As discussed in Example 27 of the specification, when different monoclonal antibodies were administered to normal mice, antibodies produced by hybridoma FERM BP-7838 or FERM BP-7939 dramatically increased the serum phosphate concentration, as shown in Figure 21A.

The specification further discloses that blood FGF-23 concentration in a patient of XLH was higher than that of normal subjects (Example 30), and that blood FGF-23 concentration increased significantly in XLH mouse model, e.g., Hyp mouse (Example 23). As demonstrated in Example 32, the serum phosphate concentration of Hyp mice was increased when a mixture of antibodies produced by hybridomas FERM BP-7838 and FERM BP-7839 was administered to Hyp mice. The *in vivo* results demonstrated that the conditions such as disorders of bone extension and bone calcification were alleviated by the administration of the mixture of the antibodies. By the same token, administration of the mixture of the antibodies to post-ovariectomy reduced-bone-mass mouse model promoted bone formation. *See* Example 34.

Accordingly, the examiner's contention that "[t]he disclosure of Itoh is sufficient to constructively reduce to practice monoclonal and polyclonal antibodies that bind amino acid residues

1-179 of FGF-23 and antagonize FGF-23 activity" is unsound because it is based on an incorrect interpretation of the prior-art teaching. Final action at page 4, lines 20-22.

In view of the foregoing, withdrawal of the anticipation rejection is warranted.

CONCLUSION

Applicants submit that the application is in condition for allowance, and they request an early indication to this effect. Examiner Skelding is invited to contact the undersigned directly, should he feel that any issue warrants further consideration.

Respectfully submitted,

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